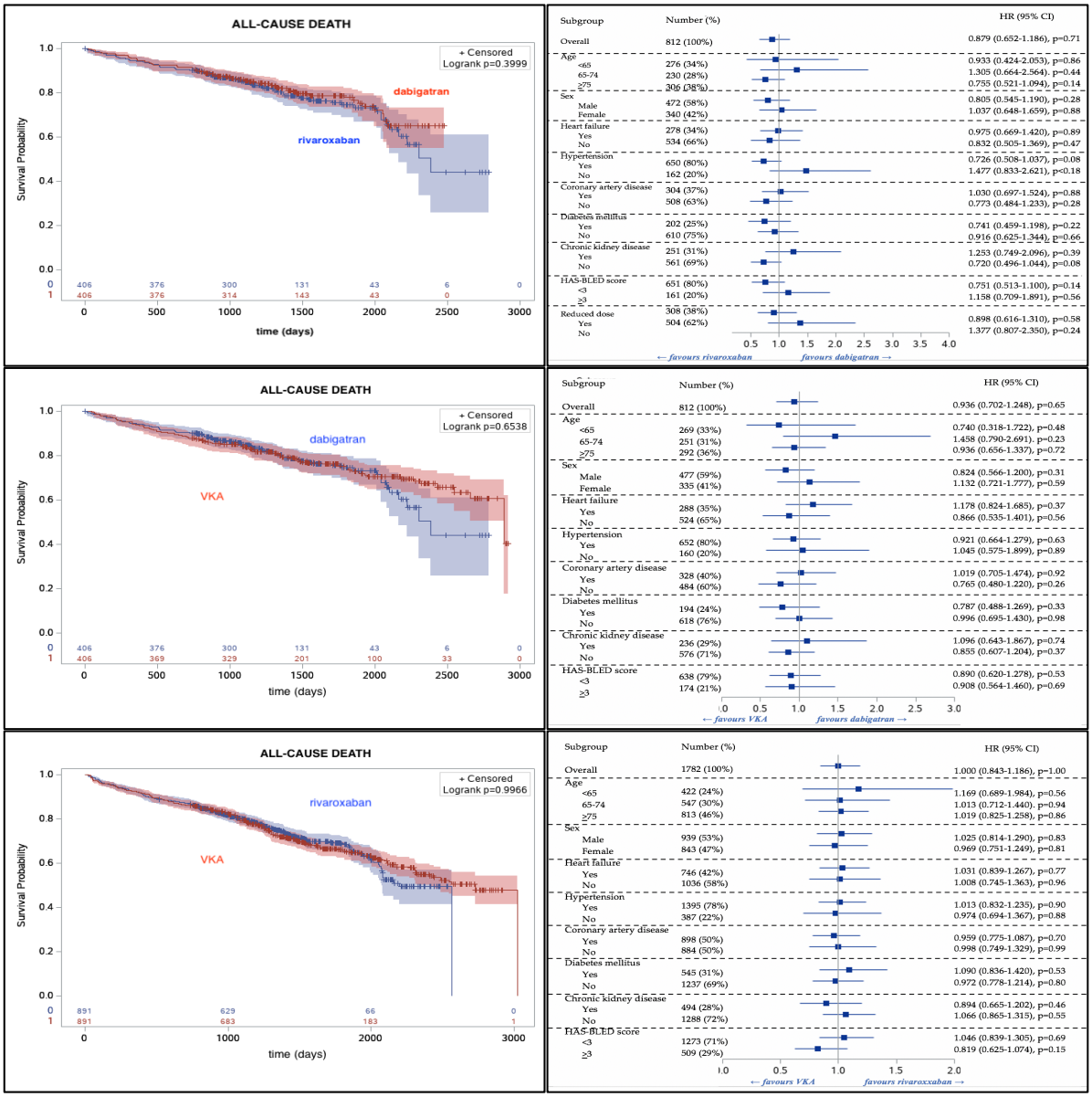
Supplementary material online

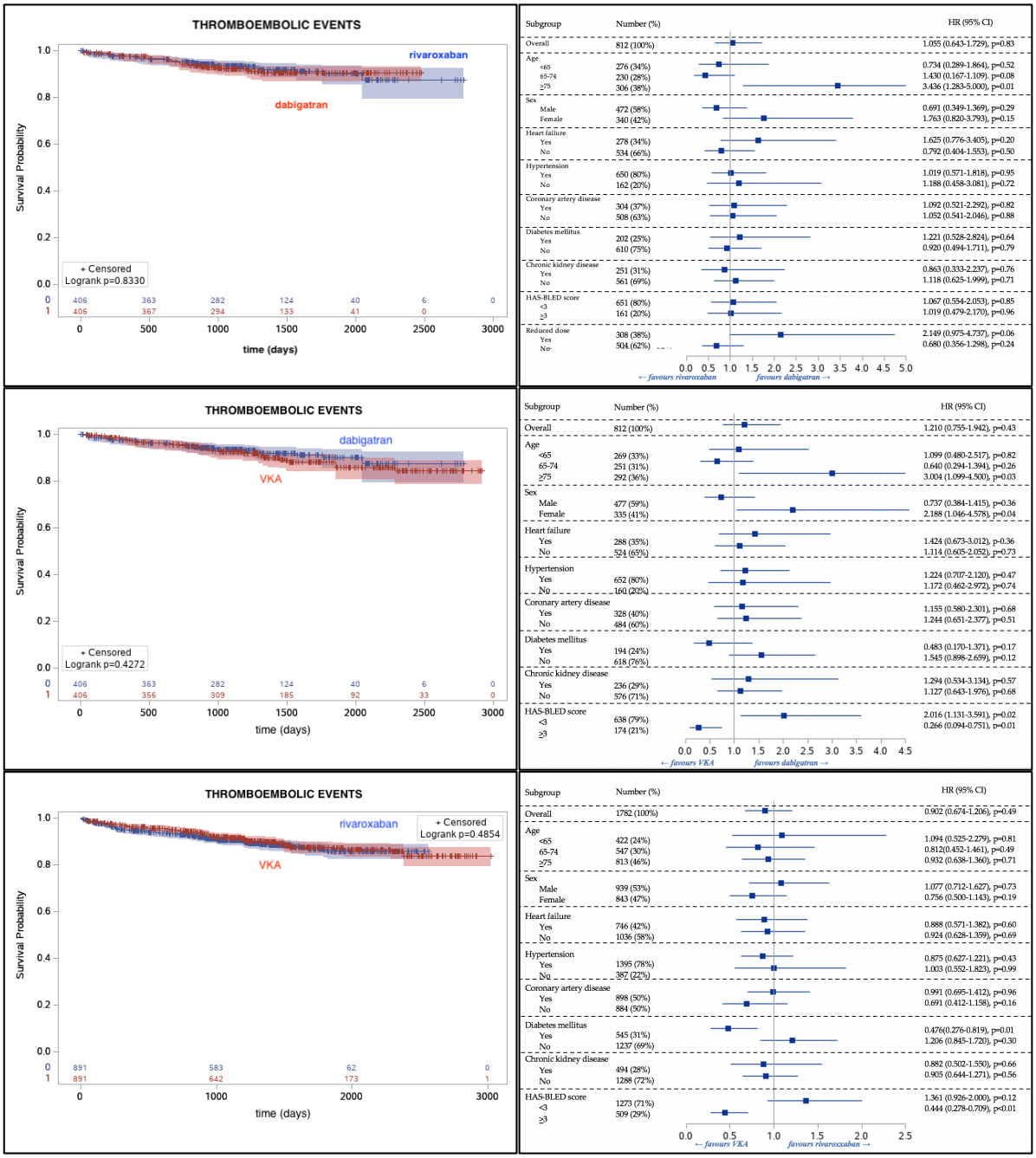
Figure S1. Kaplan-Meier analysis of time-to-events (left side) and subgroup-specific hazard ratios with 95% confidence intervals for events (right side) in patients treated with dabigatran vs rivaroxaban (upper panel) dabigatran vs VKA (middle panel) rivaroxaban vs VKA (lower panel) after propensity score matching.

A) All-cause death



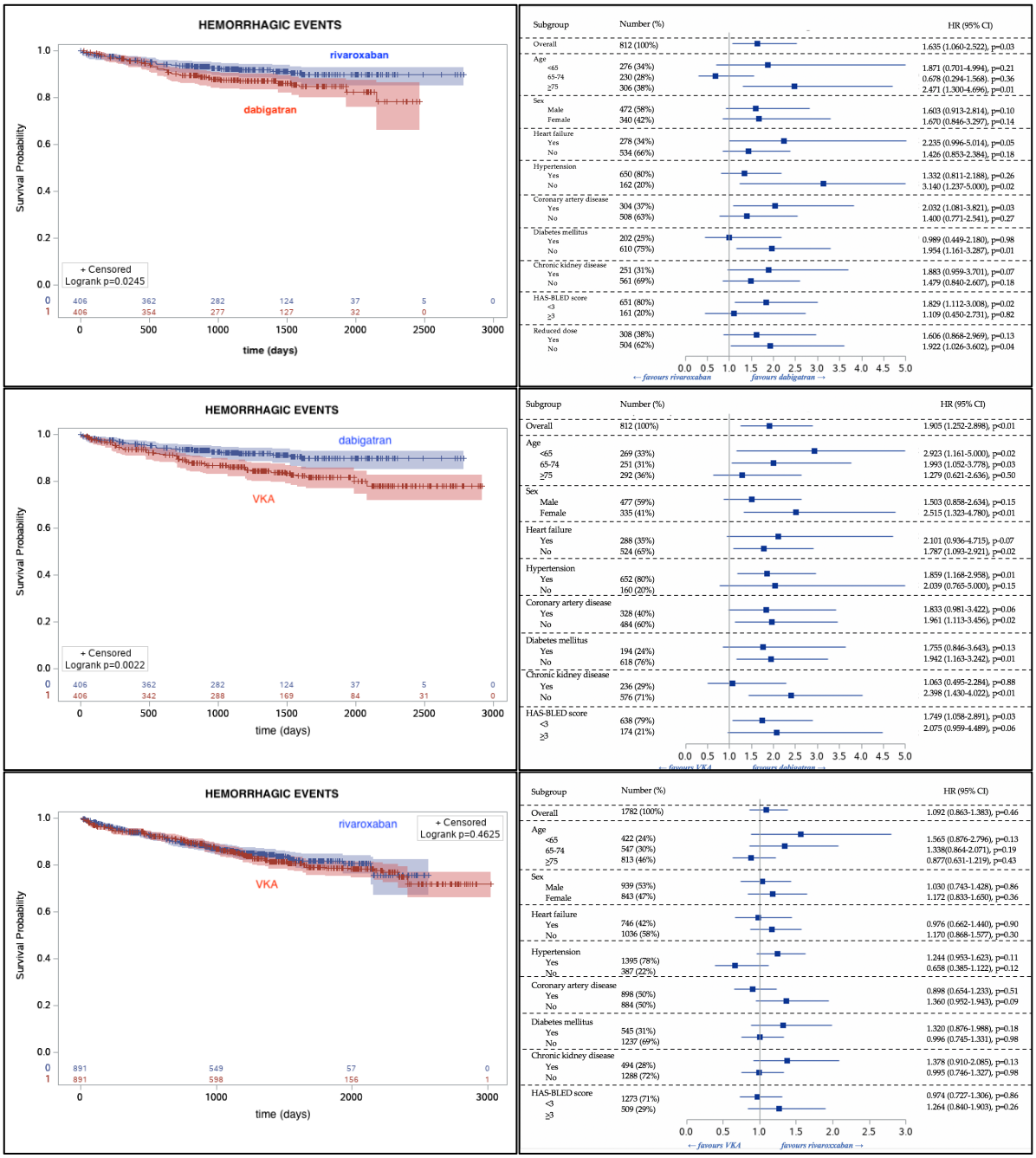
Abbreviations: VKA, vitamin K antagonist

b) thromboembolic events



Abbreviations: VKA, vitamin K antagonist

c) hemorrhagic events



Abbreviations: VKA, vitamin K antagonist

Figure S2. Thromboembolic and bleeding risk scores and their predictive value.

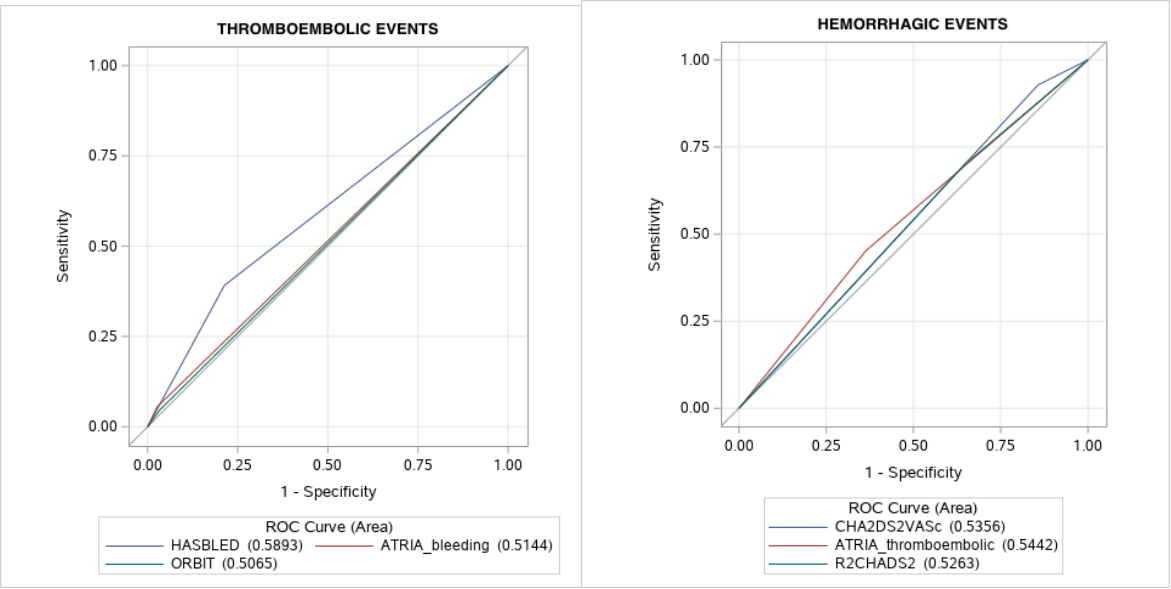


Table S1. Analyzed ICD-10 codes

Ischemic events	I63, I74.2, I74.3, I74.4, I74.5, I74.8, I74.9, I74, I65, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.8, I63.9, I67.8, I67.9, I64, I74.0, I74.1 K55.0, M31.1, N28.0, H34.1, G45.8, G45.9, G45,
Bleeding events	I85.0, I84.4, I98.3, K22.1, K25.4, K26.4, K27.0, K29.0, K29.7, K31.8, K92.0, K57.3, K57.9, K62.5, K92.1, K92.2, K25.0, K25.2, K25.6, K26.0, K26.2, K26.6, K27.2, K27.4, K27.6, K28.0, K28.2, K28.4, K28.6, K29.2, K29.3, K29.4, K29.5, K29.6, K29.8, K55.2, K57.0, K57.1, K57.2, K57.4, K57.5, K57.8, K22.6, K66.1, K76.2, K62.6, K63.3, I62.0, I62.9, I60 , I60.0, I60.1, I60.2, I60.3, I60.4, I60.5, I60.6, I60.7, I60.8, I60.9, I61, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9, I62.1, I62, S06.4, S06.5, S06.6, D62, D68.3, D69.8, D69.9, H05.2, H11.3, H21.0, H31.3, H31.4, H35.6, H43.1, H44.8, H45.0, H47.0, H92.2, I23.0, I31.2, I71.3, J94.2, M25.0, M79.8, N02, N02.0, N02.1, N02.2, N02.3, N02.4, N02.5, N02.6, N02.7, N02.8, N02.9, N42.1, N42.1, N83.7, N85.7, N89.7, N92.0, N92.1, N92.3, N92.4, N92.5, N93, N93.0, N93.8, N93.9, N95.0, O71.7, R04, R04.0, R04.1, R04.2, R04.8, R04.89, R04.9, R23.3, R31, R31.0, R31.9, R58, R58 , S26.0, S27.1, T79.2, T81.0, Y60

Table S2. Comparison of rivaroxaban and dabigatran treatment groups after propensity score matching.

Variable	Rivaroxaban (n=406)	Dabigatran (n=406)	p value
Demographics			
Age (years)	70 [61-79]	69 [62-78]	0.35
Females	174 (43%)	166 (41%)	0.62
Atrial fibrillation type			
Paroxysmal	219 (54%)	208 (51%)	0.48
Non-paroxysmal	187 (46%)	198 (49%)	
Comorbidities			
Heart failure	129 (32%)	149 (37%)	0.16
Hypertension	324 (80%)	326 (80%)	0.93
Coronary artery disease	144 (35%)	160 (39%)	0.28
Diabetes mellitus	108 (27%)	94 (23%)	0.29
Ischemic stroke/TIA/ thromboembolism	56 (14%)	58 (14%)	0.92
Haemorrhagic events	31 (7.6%)	30 (7.4%)	1.00
COPD	21 (5.2%)	28 (6.9%)	0.38
Smoking	29 (7.2%)	32 (7.9%)	0.79
Laboratory parameters			
eGFR ≤14 ml/min/1.73m2	0 (0%) *n=346*	0 (0%) *n=353*	1.00
eGFR 15-29 ml/min/1.73m2	4 (1.2%) *n=346*	3 (0.8%) *n=353*	1.00
eGFR 30-49 ml/min/1.73m2	64 (18%) *n=346*	67 (19%) *n=353*	0.85
eGFR ≥50 ml/min/1.73m2	278 (80%) *n=346*	283 (80%) *n=353*	1.00

Number provided after in italic indicates the total number of patients available for that variable.

Abbreviations: COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; TIA, transient ischemic attack

Table S3. Comparison of vitamin K antagonist and dabigatran treatment groups after propensity score matching.

Variable	VKA (n=406)	Dabigatran (n=406)	p value
Demographics			
Age (years)	69 [62-78]	69 [62-78]	0.88
Females	169 (42%)	166 (41%)	0.89
Atrial fibrillation type			
Paroxysmal	221 (54%)	208 (51%)	0.40
Non-paroxysmal	185 (46%)	198 (49%)	0.40
Comorbidities			
Heart failure	139 (32%)	149 (37%)	0.51
Hypertension	326 (80%)	326 (80%)	1.00
Coronary artery disease	168 (41%)	160 (39%)	0.62
Diabetes mellitus	100 (25%)	94 (23%)	0.68
Ischemic stroke/TIA/ thromboembolism	45 (11%)	58 (14.3%)	0.21
Haemorrhagic events	21 (5.2%)	30 (7.4%)	0.25
COPD	31 (7.6%)	28 (6.9%)	0.79
Smoking	30 (7.4%)	32 (7.9%)	0.90
Laboratory parameters			
eGFR ≤14 ml/min/1.73m2	0 (0%) *n=358*	0 (0%) *n=353*	1.00
eGFR 15-29 ml/min/1.73m2	6 (1.7%) *n=358*	3 (0.7%) *n=353*	0.51
eGFR 30-49 ml/min/1.73m2	59 (16%) *n=358*	67 (19%) *n=353*	0.50
eGFR ≥50 ml/min/1.73m2	293 (82%) *n=358*	283 (80%) *n=353*	0.49

Number provided after in italic indicates the total number of patients available for that variable.

Abbreviations: COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; TIA, transient ischemic attack; VKA, vitamin K antagonist

Table S4. Comparison of rivaroxaban and vitamin K antagonist treatment groups after propensity score matching.

Variable	Rivaroxaban (n=891)	VKA (n=891)	p value
Demographics			
Age (years)	74 [65-81]	72 [65-80]	0.08
Females	420 (47%)	423 (47%)	0.92
Atrial fibrillation type			
Paroxysmal	467 (52%)	463 (52%)	0.89
Non-paroxysmal	424 (48%)	428 (48%)	0.89
Comorbidities			
Heart failure	381 (43%)	365 (41%)	0.47
Hypertension	689 (77%)	706 (79%)	0.36
Coronary artery disease	447 (50%)	451 (51%)	0.89
Diabetes mellitus	274 (31%)	271 (30%)	0.92
Ischemic stroke/TIA/ thromboembolism	157 (18%)	166 (19%)	0.63
Haemorrhagic events	98 (11%)	83 (9.3%)	0.27
COPD	114 (13%)	101 (11%)	0.38
Smoking	57 (6.4%)	55 (6.2%)	0.92
Laboratory parameters			
eGFR ≤14 ml/min/1.73m2	3 (0.4%) *n=831*	1 (0.1%) *n=829*	0.62
eGFR 15-29 ml/min/1.73m2	18 (2.2%) *n=831*	14 (1.7%) *n=829*	0.59
eGFR 30-49 ml/min/1.73m2	178 (21%) *n=831*	158 (19%) *n=829*	0.25
eGFR ≥50 ml/min/1.73m2	632 (76%) *n=831*	656 (79%) *n=829*	0.22

Number provided after in italic indicates the total number of patients available for that variable.

Abbreviations: COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; TIA, transient ischemic attack; VKA, vitamin K antagonist

Table S5. Distribution of direct oral anticoagulants according the recommendation for patients receiving reduced (A) and standard (B) dosing.

A. Reduced doses of direct oral anticoagulants		
Variable	**Dabigatran (n=177)**	**Rivaroxaban (n=379)**
Correct prescription		
All	**116 (66%)**	**250 (66%)**
Recommended indications for dose reduction		
- eGFR 30-49ml/min/1.73m2	101 (57%)	163 (43%)
- eGFR 15-49ml/min/1.73m2	24 (13%)	Not applicable
- Age ≥ 80 years	Not applicable	163 (43%)
- eGFR 30-49ml/min/1.73m2 + age ≥ 80 years	51 (29%)	Not applicable
Indications to be considered (≥ 2 below indications)	26 (15%)	Not applicable
	15 (8.5%)	87 (23%)
Incorrect prescription		
All	**52 (29%)**	**122 (32%)**
Unknown reason	28 (16%)	25 (6.6%)
Indications to be considered	24 (13%)	97 (26%)
- HAS-BLED ≥ 3	2 (1.1%)	5 (1.3%)
- Age ≥ 75 years	17 (9.6%)	83 (22%)
- NSAIDs and/or APT drugs	2 (1.1%)	7 (1.8%)
- Amiodarone	3 (1.7%)	2 (0.5%)
Unknown appropriate prescriptions		
No data regarding CrCl or type of DHP-CCB	**9 (5.1%)**	**7 (1.8%)**

B. Standard doses of direct oral anticoagulants		
Variable	**Dabigatran (n=224)**	**Rivaroxaban (n=502)**
Incorrect prescription		
Recommended indications for dose reduction	**26 (12%)**	**35 (7.0%)**
- eGFR 30-49ml/min/1.73m2	16 (7.1%)	Not applicable
- eGFR 15-49ml/min/1.73m2	Not applicable	35 (7.0%)
- Age $\geq$ 80 years	8 (3.6%)	Not applicable
- eGFR 30-49ml/min +age $\geq$ 80 years	2 (0.9%)	Not applicable
Correct prescription		
All	**153 (68%)**	**415 (83%)**
Unknown appropriate prescriptions		
No data regarding eGFR or type of DHP-CCB	**45 (20%)**	**52 (10%)**

Abbreviations: DHP-CCB – dihydropyridine calcium canal blockers, eGFR, estimated glomerular filtration rate; NSAID - nonsteroidal anti-inflammatory drugs

Table S6. Analysis of time-to-major adverse events, all-cause death, thromboembolic and hemorrhagic events for patients treated with appropriate and inappropriate reduced and/or standard NOAC doses.

	Major adverse event	All-cause death	Thromboembolic events	Haemorrhagic events
	HR [95% CI]	HR [95% CI]	HR [95% CI]	HR [95% CI]
Dabigatran (n=401)				
Incorrect dose	1.140 (0.733-1.772)	1.023 (0.600-1.744)	1.450 (0.619-3.398)	1.175 (0.510-2.708)
Correct dose	reference	reference	reference	reference
Dabigatran reduced (n=177)				
Incorrect dose	0.644 (0.382-1.087)	0.552 (0.302-1.012)	1.540 (0.434-5.459)	0.591 (0.196-1.782)
Correct dose	reference	reference	reference	reference
Dabigatran standard (n=224)				
Incorrect dose	1.715 (0.743-3.957)	1.674 (0.531-5.272)	1.742 (0.506-5.999)	2.393 (0.666-8.459)
Correct dose	reference	reference	reference	reference
Rivaroxaban (n=881)				
Incorrect dose	1.250 (0.969-1.613)	**1.624 (1.209-2.181)**	0.964 (0.554-1.675)	0.922 (0.572-1.486)
Correct dose	reference	reference	reference	reference
Rivaroxaban reduced (n=379)				
Incorrect dose	0.769 (0.567-1.043)	0.809 (0.573-1.143)	0.592 (0.301-1.164)	NA
Correct dose	reference	reference	reference	reference
Rivaroxaban standard (n=502)				
Incorrect dose	1.576 (0.927-2.681)	**2.754 (1.497-5.068)**	1.502 (0.537-4.195)	0.832 (0.280-2.658)
Correct dose	reference	reference	reference	reference
NOAC (n=1282)				
Incorrect dose	1.211	**1.429**	1.068	0.956

	(0.971-1.510)	**(1.104-1.848)**	(0.673-1.696)	(0.633-1.446)
Correct dose	reference	reference	reference	reference
NOAC reduced (n=556)				
Incorrect dose	**0.744 (0.572-0.967)**	**0.739 (0.549-996)**	0.740 (0.410-1.335)	0.644 (0.393-1.053)
Correct dose	reference	reference	reference	reference
NOAC standard (n=726)				
Incorrect dose	1.515 (0.971-2.364)	2.212 (1.293-3.783)	1.571 (0.716-3.447)	1.211 (0.971-1.510)
Correct dose	reference	reference	reference	reference

Abbreviations: CI, coincidence interval; NOAC, non-vitamin K oral anticoagulant; HR, hazard ratio